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भौगोलिक संकेत
PATENTS / DESIGNS /
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सत्यमेव जयते

भारत सरकार /GOVERNMENT OF INDIA
पेटेन्ट कार्यालय /THE PATENT OFFICE
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THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of the Patent Application and Provisional Specification filed on 21/04/2003 in respect of Patent Application No.392/MUM/2003 of Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, Maharashtra State,India, an Indian Company registered under the Companies Act 1956.

This certificate is issued under the powers vested in me under Section 147 (1) of the Patents Act, 1970.

Dated this 03rd day of June 2008.

(A.T. PATRE)
ASSTT.CONTROLLER OF PATENTS & DESIGNS.

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

[See sections 5(2), 7, 54 and 135 and rule 33A]

1. We, Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, Maharashtra State, India an Indian Company registered under the Companies Act 1956

2. hereby declare:-

a) that we are in possession of an invention titled 'Antimicrobial Oxazolidinones with Improved Pharmacokinetic Profile and Safety Advantages'.
b) that the Provisioal Specification relating to this invention is filed with this application.
c) that there is no lawful ground for objection to the grant of a patent to us.

3. further declare that the inventor (s) for the said invention are:

a) Dr. Noel John de Souza, Dr. Prasad Keshav Deshpande

b) Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, Maharashtra State, India.

c) All Indian Nationals

4. We, claim the priority from the application(s) filed in convention countries, particulars of which are as follows :

Not applicable

5. I/We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which I/we are the applicant/patentee:

Not applicable.

6. I/We state that the application is divided out of my/our application, the particulars of which are given below and pray that this application deemed to have been filed on ____ under section 16 of the Act.

Not applicable.

ORIGIN

392/MUM/2003
21 APRIL 2003

392/MUM/2003
21/4/2003

ORGN

Received Rs. 5000/- by Cash
21/4/03
Vide Entry No. 2941 in the Register of Receipts, Bombay.
for
22.04.03

भारत सरकार पेटेन्ट कार्यालय शाखा
21 APRIL 2003
मुंबई

7. That we are the assignee or legal representative of the true and first inventors.

8. That our address for service in India is as follows:

   Wockhardt Limited
   Wockhardt Towers
   Bandra-Kurla Complex
   Bandra (E)
   MUMBAI 400 051
   Tel. No. 022-6534444
   Fax 022-6534242

9. Following declaration was given by the inventor(s):

   We the true and first inventors for this invention declare that the applicant Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051 herein is our assignee.

Dr. Noel John de Souza _____

Dr. Prasad Keshav Deshpande _____

Dated this 17th day of April 2003

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Following are the attachment with the application:

    a) Provisional Specification – 3 copies
    b) Form 2
    c) Form 3

We request that a patent may be granted to us for the said invention.

Dated this 17th day of April 2003

Dr N J de Souza
Director-R&D

To

The Controller of Patents,
The Patents Office Branch, Mumbai.

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
(See section 10)

1. **Title: 'ANTIMICROBIAL OXAZOLIDINONES WITH IMPROVED PHARMACOKINETIC PROFILE AND SAFETY ADVANTAGES'**

2. Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East) Mumbai – 400 051, Maharashtra State, India, an Indian Company registered under the Companies Act 1956

The following specification describes the nature of the invention and the manner in which it is to be performed.

ORIGINAL

Antimicrobial Oxazolidinones with Improved Pharmacokinetic Profile and Safety Advantages

Field of the Invention:

The present invention relates to the field of novel cyanoalkylpiperidinophenyl oxazolidinones having antibacterial activity and favourable pharmacokinetic and safety profiles. The invention also relates to processes for making the compounds, to pharmaceutical compositions containing the compounds and to methods of treating bacterial infections with the compounds.

Background of Invention:

Oxazolidinones represent a novel chemical class of synthetic antimicrobial agents. Following a chequered historical development since about the early-1980s, a watershed event took place with the clinical development and release for medical use in the late 2000s of the first representative, Linezolid, of this class[1,2] This advance enabled the profiling of the unique properties of the members of this class, which is that they display activity against important Gram-positive human and veterinary pathogens including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin resistant enterococci (VRE) and β-lactam resistant *Streptococcus pneumoniae* (PRSP). The oxazolidinones also show activity against Gram-negative aerobic bacteria and Gram-positive and Gram-negative anaerobes[3].

The deficiencies of this class of oxazolidinones have also surfaced. They are inactive against Enterobacteriaceae[4]. They are generally bacteriostatic and do not display activity at a useful level against aerobic fastidious Gram-negative pathogens, as well as Gram-negative anaerobes. Moreover their potency for atypical respiratory pathogens such as *Mycoplasma pneumoniae, M. hominis, Ureaplasma urealyticium* and *Chlamydia* species is of a borderline range which could result into unacceptable clinical efficacy for the treatment of respiratory tract infections[3].

One major limitation of Linezolid as representative of the class of oxazolidinones is that its pharmacokinetics in human is such that the package insert in the marketed product for its clinical usage recommends a twice-a-day administration[4]. A twice-a-day dosing is considered inconvenient in terms of maintaining adequate blood levels of the antibacterial sufficient to eradicate the infection. There is a dire need for oxazolidinones with a pharmacokinetic profile that would enable bioavailability of the drug in mammals in such amounts that the dosing can be reduced to once-a-day. The clinical significance of drugs with once-a-day dosing requirement is in the form of improved patient compliance leading to superior clinical efficacy, minimising the risk of therapeutic failure due to emergence of resistant strains and the reduced probability of drug-drug interactions for severely ill patients simultaneously on multidrug regimens.

Other limitations that have appeared through the clinical development and use of Linezolid, and its potential successors in development, are that the class has a propensity to induce meyelosuppression with consequent anemia, leukopenia, pancytopenia and thrombocytopenia [5]. Inhibition of monoamine oxidase by oxazolidinones has prompted a recommendation made to clinicians that clinical use of members of this class be done with caution during concomitant usage of adrenergic or serotonergic agents and selective serotonin reuptake inhibitors[6].

Our pending US Application No. 60/395,164 discloses a novel series of oxazolidinones which display increased potency, and incorporate bactericidal activity, in contrast to the earlier-described bacteriostatic activity of Linezolid and literature described oxazolidinones, against Linezolid-sensitive/-resistant strains, thus indicating a differential binding at the conventional site/s of the ribonucleoprotein and/or targeting multiple such receptor sites.

The same above mentioned application discloses other information pertaining to patents cited in the literature, without a comment made that they have any bearing on the said application.

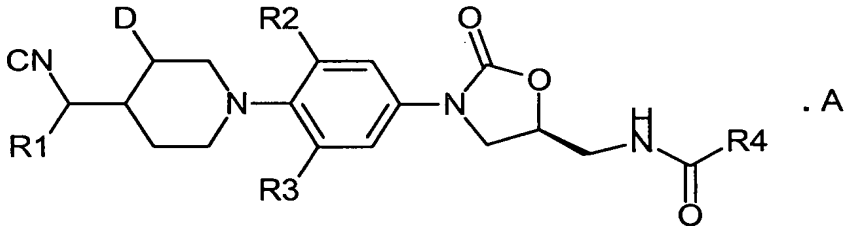
US Patent 5,668,286 and related family Patent EP 0750 618 B1 disclose substituted piperidinophenyl oxazolidinones and their usefulness as antimicrobial agents. The MIC (minimum inhibitory concentration) data for compounds of the invention against typical organisms has been reported. ED_{50} values determined by a murine assay procedure (*in vivo*) has been reported for four compounds on oral administration. No data has, however, been provided on their pharmacokinetic profile or on their safety profiles, in particular on their ability to cause myelosuppression. None of the compounds in the instant invention are actually prepared or described in US Patent 5,668,286 and EP 0750 618 B1, which is herein done for the first time and has thus enabled profiling the efficacy, pharmacokinetic behaviour and safety advantages of the compounds of this invention in comparison to the compounds described in US Patent 5,668,286 and EP 0750 618 B1.

Summary of the Invention:

The object of the present invention is to provide novel cyanoalkylpiperidinophenyl oxazolidinones or pharmaceutically acceptable salts or complexes thereof, which have high antimicrobial activities with favourable pharmacokinetic profiles and safety advantages.

The present inventors conducted intensive studies in order to accomplish the above object. As a result useful and novel oxazolidinone derivatives are found and the present invention has been accomplished on the basis of the findings.

The present invention provides cyanoalkylpiperidinophenyl oxazolidinones represented



. A

by the general Formula-I

Formula-I

Wherein,

R_1 is

-H;

C1-C8 alkyl;

substituted alkyl;

-COOH;

-CN.

R_2 and R_3 are the same or different and are H or fluorine;

R4 is

H;

C1-C8 alkyl;
C1-C8 alkoxy.

D is
H;
C1-C8 alkyl;
fluorine.

A is
nothing;
complex forming agent;
organic base;
amino acid.

The present invention also provides an antimicrobial agent that contains the oxazolidinone derivative or a pharmacetuically acceptable salt thereof as an effective ingredient. The antimicrobial agent containing the effective ingredient of the present invention can be used for treatment or prevention of infectious diseases. The term "treatment" as used herein means partial or total avoidance of symptoms of a disease in a patient who, according to a doctor's diagnosis, may suffer from the disease or a related state unless the preventive measure is taken.

This invention provides novel oxazolidinone derivatives useful as preventatives and therapeutics for infectious diseases. The compounds of this invention have excellent antimicrobial action against various human and veterinary pathogens, including multiply-resistant staphylococci and streptococci, as well as anaerobic organisms such as bacteroides and clostridia species, and acid-fast *Mycobacterium tuberculosis and M. avium.* In particular, a special embodiment of the invention is that the compounds of the invention have a pharmacokinetic profile which provides a hitherto-unavailable once-a-day treatment potential for this class of oxazolidinone antiinfective agent. Another embodiment of the invention is that the compounds of the invention provides greater

safety in respect of myelosuppression, known to be a class-specific hazard for this class of oxazolidinone antiinfective agent.

Detailed Description of terms:

"C1-C8 alkyl" means carbon atom chains having C1-C8 number of carbon atoms such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl.
"Substituted alkyl" means C1-C8 alkyl, bearing substituents like one or more hydroxy, methane sulfonyloxy.

C1-C8 alkyloxy stands for methoxy, ethoxy, propoxy, butoxyy, pentoxy, hexyloxy, heptyloxy, octyloxy and isomeric forms thereof.

Complex forming agents stands for agents which can form complex with oxazolidinones such as cyclodextrins.
Cyclodextrin can be selected from α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin.

β-Cyclodextrin can be further selected from methyl-β-cyclodextrin, 2-hydroxy-propyl-β-cyclodextrin (2-HP-β-cyclodextrin), 3-hydroxy-propyl-β -cyclodextrin (3-HP-β-cyclodextrin), sulfobutylether-β-cyclodextrin.

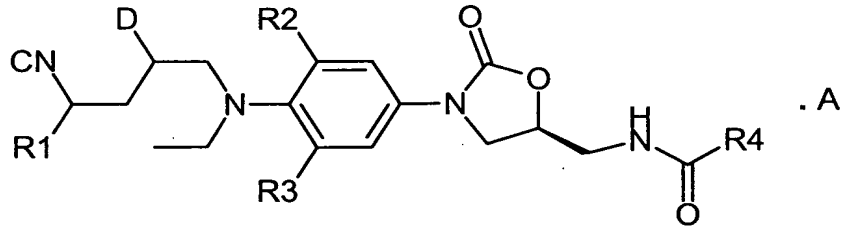
Organic bases stands for bases such as ethanolamine, guanidine etc.
Amino acid stands for dibasic amino acids such as racemic or optically active arginine, and lysine.

The preferred absolute configuration at C-5 of the oxazolidinone ring of compounds claimed in this invention is as represented in the structure of Formula I. This absolute configuration is called (S) under the Cahn-Ingold-Prelog nomenclature system. It is this (S)-enantiomer which is pharmacologically active. The racemic mixture is useful in the same way and for the same purpose as the pure (S)-enantiomer; the difference is that twice as much racemic material must be used to produce the same antibacterial effect.

Depending on substituents, the compounds of this invention may exist in geometric, optical and other isomeric forms and this invention embraces any of these isomers.

Particular preferred examples of the oxazolidinone derivatives represented by the general Formula I are as in the following Table 1 (prefixed by compound numbers) and the subsequent list of preferred compounds.

Table-1



. A

Entry No	R_1	D	R_2	R_3	R_4	A
1	-H	-H	-H	-H	$-CH_3$	Nothing
2	-H	-H	-H	-F	$-CH_3$	Nothing
3	-H	-H	-H	-F	$-CH_3$	3-HP-β-cyclodextrin
4	-H	-H	-H	-F	$-CF_3$	Nothing
5	-H	-H	-H	-F	$-OC_2H_5$	Nothing
6	-H	-H	-H	-F	$-O\text{-}i\text{-}C_4H_9$	Nothing
7	-H	-H	-H	-F	$-O\text{-}t\text{-}C_4H_9$	Nothing
8	-H	$-CH_3$	-H	-F	$-CH_3$	Nothing
9	-H	-F	-H	-F	$-O\text{-}i\text{-}C_4H_9$	Nothing
10	$-CH_3$	-H	-H	-F	$-CH_3$	Nothing
11	$-C_2H_5$	-H	-H	-F	$-CH_3$	Nothing
12	$-C_3H_7$	-H	-H	-F	$-CH_3$	Nothing
13	$-CH_2OH$	-H	-H	-F	$-CH_3$	Nothing
14	$-CH_2OSO_2CH_3$	-H	-H	-F	$-CH_3$	Nothing
15	-COOH	-H	-H	-F	$-CH_3$	Nothing
16	-CN	-H	-H	-F	$-CH_3$	Nothing

List of preferred compounds:

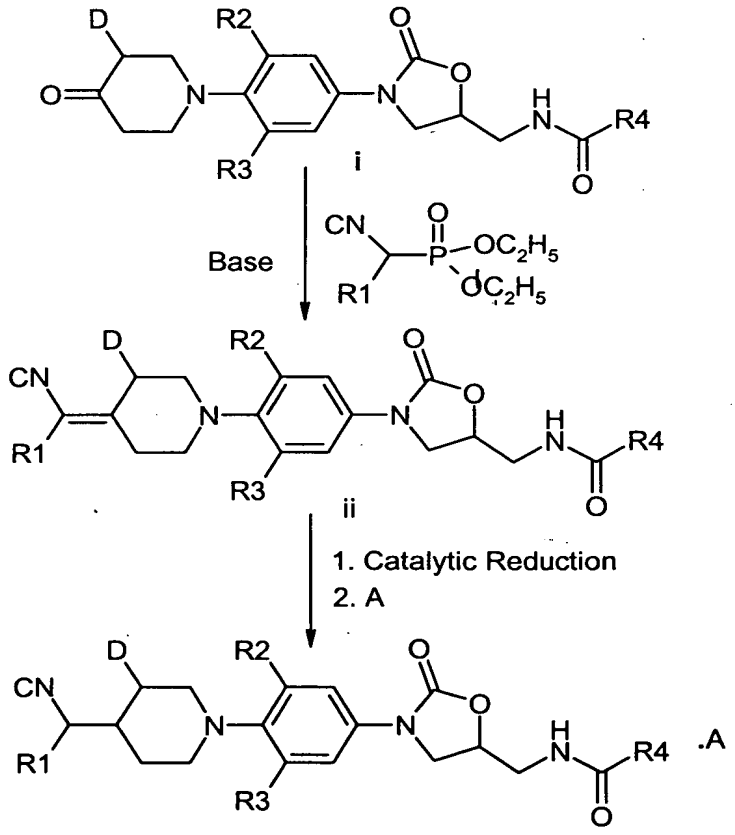
1. (S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide;
2. (S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide;
3. (S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide, inclusion complex with 3-hydroxy-propyl-β-cyclodextrin.
4. (S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-trifluoroacetamide;
5. (S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-ethylcarbamate;
6. (S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}- iso-butylcarbamate;
7. (S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-t-butylcarbamate;
8. (S)-N-{3-[4-((4-cyanomethyl)-3-methyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide;
9. (S)-N-{3-[4-((4-cyanomethyl)-3-fluoro-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-isobutylcarbamate;
10. (S)-N-{3-[4-(4-(1-cyanoethyl)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide;
11. (S)-N-{3-[4-(4-(1-cyanopropyl)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide;
12. (S)-N-{3-[4-(4-(1-cyanobutyl)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide;
13. (S)-N-{3-[4-(4-(1-cyano-2-hydroxyethyl)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide;
14. (S)-N-{3-[4-(4-(1-cyano-2-methanesulfonyloxyethyl)--piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide;

15. (S)-N-{3-[4-(4-(1-cyano-1-hydroxycarbonyl)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide;
16. (S)-N-{3-[4-(4-(1,1-dicyanomethyl)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide;

The compounds represented by the general Formula I can be prepared by the method of reaction Scheme 1.

All the starting materials are prepared by procedures described in this Scheme-1 or by procedures that would be well known to one of ordinary skill in organic chemistry. The variables used in Scheme-1 are as defined above. Optically pure material could be obtained by one of a number of asymmetric synthesis or alternatively by resolution from a racemic mixture.

Scheme-1



In accordance with Scheme-1 the piperidone intermediate (S)-N-{3-[3-fluorlo-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (i), (cf. US 5,668,286, column 15, Example 3) or any other substituted piperidone intermediate with appropriate values for the R_1, R_2, R_3, R_4 and D substituents in accordance with the Formula I is reacted with an appropriate Wittig reagent optionally in the presence of a base such as triethylamine, diispropylethylamine, sodium hydride, lithium diisopropylamine or n-butyl lithium in a suitable solvent such as diethylether, tetrahydrofuran or benzene at a temperature between -10 ^{0}C to 50 ^{0}C to provide the cyanoalkene compound ii.

The compound ii upon further reduction in the presence of a catalyst such as 5% palladium on carbon, 10% palladium on carbon, palladium hydroxide at atmospheric pressure of hydrogen gas or alternatively in the presence of hydrogen sources such as ammonium formate, cyclohexene in a suitable solvent such as ethyl acetate, tetrahydrofuran, methanol, or mixture thereof at a temperature between 20 ^{0}C to 50 ^{0}C provided the cyanoalkyl compound of the Formula I of the invention. This compound was optionally treated with a suitable complex forming agent such as α-cyclodextrin, β-cyclodextrin, γ-cyclodextrin or with an organic base such as diethanolamine or guanidine in a suitable solvent such as water, methanol, acetone and mixture thereof to provide a cyclodextrin complex of a compound of Formula I of the invention.

General Methods

General method to prepare oxazolidinone:

A. Compound of Formula I is prepared by

i) stirring the piperidone intermediate (S)-N-{3-[3-fluoro-4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (i) (cf. US 5,668,286, column 15, Example 3) or any other substituted piperidone intermediate with appropriate values for the R_1, R_2, R_3, R_4 and D substituents in accordance with the Formula I with an appripriate Wittig reagent optionally in the presence of a suitable base

such as triethylamine, diispropylethylamine, sodium hydride lithium diisopropylamine or n-butyl lithium preferably triethylamine in a solvent such as diethylether, tetrahydrofuran or benzene preferably tetrahydrofuran at a temperature between –10 ^{0}C to 50 ^{0}C preferably 20 ^{0}C - 40 ^{0}C to provide the corresponding cyanoalkene compound ii.

ii) stirring the cyanoalkenyl compound ii in the presence of catalyst such as 5% palladium on carbon, 10% palladium on carbon, palladium hydroxide preferably 10% palladium on carbon; at atmospheric pressure of hydrogen gas or alternatively in the presence of a hydrogen source such as ammonium formate, cyclohexene preferably in the presence of hydrogen gas; in a suitable solvent such as ethyl acetate, tetrahydrofuran, methanol, or mixture thereof preferably tetrahydrofuran at a temperature between 20 ^{0}C to 50 ^{0}C to provide the cyanoalkyl compound of the Formula I of the invention.

iii) Optionally stirring the cyanoalkyl compound obtained in step ii with a suitable complex forming agent such as α-cyclodextrin, β-cyclodextrin, substituted β-cyclodextrin, γ-cyclodextrin preferably with substituted β-cyclodextrin; or with an organic base such as diethanol amine or guanidine in a suitable solvent such as water, methanol, acetone and mixture thereof preferably water; at a temperature between 30 ^{0}C to 60 ^{0}C for 2 to 48 hours preferably 24 hours followed by evaporating the solvent under reduced pressure and drying the compound under vacuum to provide a cyclodextrin complex of the compound of Formula I of the invention.

Method –1

Preparation of 1-cyano substituted alkyl oxazolidinones of the invention

Step-1: Preparation of (S)-N-{3-[4-(4-(1-cyano substitued /unsubstituted alkylidene)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide/-alkylcarbamate:

A suspension of suitably substituted diethyl cyanomethyl phosphonate (49 mmol), lithium bromide (49 mmol) and triethyl amine (49 mmol) in dry tetrahydrofuran was stirred for 30 minutes at a temperature between 20 to 50^{0}C. A solution of (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-3-fluoro/desfluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide/-alkylcarbamate in dry tetrahydrofuran was added in one lot to the suspension. The reaction mixture was stirred for an additional 2 – 5 hours. The reaction mixture was neutralized with 0.5 N aqueous hydrochloric acid. The mixture was extracted with ethyl acetate and the combined ethyl acetate extracts were evaporated to dryness under vacuum. The crude product was chromatographed on silica gel to afford the desired alkylidene oxazolidinone compounds.

Step-2: Preparation of (S)-N-{3-[4-(4-(1-cyano substitued/unsubstituted alkyl)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide/ -alkylcarbamate:

A clear solution made of the compound from step i in tetrahydrofuran and 10% palladium on carbon was stirred under atmospheric hydrogen pressure at a temperature between 20 to 50^{0}C.

After completion of the reaction the catalyst was filtered and the filtrate was concentrated to dryness under vacuum. The product thus obtained was chromatographed on silica gel to provide the 1-cyano substituted alkyl oxazolidinones of the invention.

Method –2

Preparation of 3-hydroxy-propyl-β-cyclodextrin inclusion complex with oxazolidinone of the invention in a molar ratio 1:1.12 or 1:2.0

To a clear solution of 3-HP-β-CD (0.112 mmol or 0.2 mmol) in 10 to 15 ml of distilled water, was charged an oxazolidinone of the invention (0.1 mmol) at a temperature between 20 to 50^{0}C under stirring. The suspension was stirred at 40 to 60^{0}C temperature for 0.5 to 4 hours to obtain a clear solution. The clear solution was allowed

stand at a temperature between 20 to 40 ^{0}C for 12 to 24 hours. The reaction mixture was filtered and filtrate was evaporated under vacuum at a temperature below 60 ^{0}C to provide a compound of the invention, typically in 80 to 98% yield.

The compounds of the invention are useful for the treatment of microbial infections in humans and other warm blooded animals by either parenteral, oral or topical administration.

The present invention encompasses certain compounds, dosage forms, and methods of administering the compounds to a human or other animal subject. Specific compounds and compositions to be used in the invention must, accordingly, be pharmaceutically acceptable. As used herein, such a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

The pharmaceutical compositions are prepared according to conventional procedures used by persons skilled in the art to make stable and effective compositions. In the solid, liquid, parenteral and topical dosage forms, an effective amount of the active compound or the active ingredient is any amount, which produces the desired results.

For the purpose of this invention the pharmaceutical compositions may contain the active compounds of the invention, their derivatives, salts and hydrates thereof, in a form to be administered alone, but generally in a form to be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Suitable carriers which can be used are, for example, diluents or excipients such as fillers, extenders, binders, emollients, wetting agents, disintegrants, surface active agents and lubricants which are usually employed to prepare such drugs depending on the type of dosage form.

Any suitable route of administration may be employed for providing the patient with an effective dosage of the compound of the invention their derivatives, salts and hydrates

thereof. For example, oral, rectal, parenteral (subcutaneous, intramuscular, intravenous), transdermal, topical and like forms of administration may be employed. Dosage forms include (solutions, suspensions, etc) tablets, pills, powders, troches, dispersions, suspensions, emulsions, solutions, capsules, injectable preparations, patches, ointments, creams, lotions, shampoos and the like.

The prophylactic or therapeutic dose of the compounds of the invention, their derivatives, salts or hydrates thereof, in the acute or chronic management of disease will vary with the severity of condition to be treated, and the route of administration. In addition, the dose, and perhaps the dose frequency, will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range, for the compounds of the invention, the derivatives, salts or hydrates thereof, for the conditions described herein, is from about 200 mg to about 1500 mg, in single or divided doses. Preferably, a daily dose range should be between about 400 mg to 1200 mg, in single or divided dosage, while most preferably a daily dose range should be between about 500 mg to about 1000 mg in divided dosage. While intramuscular administration may be a single dose or up to 3 divided doses, intravenous administration can include a continuous drip. It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient's response. The term "an amount sufficient to eradicate such infections but insufficient to cause undue side effects" is encompassed by the above – described dosage amount and dose frequency schedule. A specific embodiment of this invention is that the pharmacokinetic profile of a compound of the invention is such that it permits administration of a dosage schedule which is a much-desired once-a-day dosing, a schedule not so far advocated for the only currently available drug in the market. A further embodiment of this invention is that the once-a-day dosage schedule confirs safety advantages in respect of the phenomenon of myelosuppression described as an attribute of these class of compounds which needs to be avoided.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, or aerosol sprays, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

The compositions of the present invention include compositions such as suspensions, solutions, elixirs, aerosols, and solid dosage forms. Carriers as described in general above are commonly used in the case of oral solid preparations (such as powders, capsules and tablets), with the oral solid preparations being preferred over the oral liquid preparations. The most preferred oral solid preparation is tablets.

Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. Examples of suitable carriers include excipients such as lactose, white sugar, sodium chloride, glucose solution, urea, starch, calcium carbonate, kaolin, crystalline cellulose and silicic acid, binders such as water, ethanol, propanol, simple syrup, glucose, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate and polyvinyl pyrrolidone, disintegrants such as dried starch, sodium alginate, agar powder, laminaria powder, sodium hydrogen carbonate, calcium carbonate, Tween (fatty acid ester of polyoxyethylenesorbitan), sodium lauryl sulfate, stearic acid monoglyceride, starch, and lactose, disintegration inhibitors such as white sugar, stearic acid glyceryl ester, cacao butter and hydrogenated oils, absorption promoters such as quaternary ammonium bases and sodium lauryl sulfate, humectants such as glycerol and starch, absorbents such as

starch, lactose, kaolin, bentonite and colloidal silicic acid, and lubricants such as purified talc, stearic acid salts, boric acid powder, polyethylene glycol and solid polyethylene glycol.

The tablet, if desired, can be coated, and made into sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, or tablets comprising two or more layers.

If desired, tablets may be coated by standard aqueous or non-aqueous techniques.

In molding the pharmaceutical composition into pills, a wide variety of conventional carriers known in the art can be used. Examples of suitable carriers are excipients such as glucose, lactose, starch, cacao butter, hardened vegetable oils, kaolin and talc, binders such as gum arabic powder, tragacanth powder, gelatin, and ethanol, and disintegrants such as laminaria and agar.

In molding the pharmaceutical composition into a suppository form, a wide variety of carriers known in the art can be used. Examples of suitable carriers include polyethylene glycol, cacao butter, higher alcohols, gelatin, and semi-synthetic glycerides.

A second preferred method is parenterally for intramuscular, intravenous or subcutaneous administration.

A third preferred route of administration is topically, for which creams, ointments, shampoos, lotions, dusting powders and the like are well suited. Generally, an effective amount of the compound according to this invention in a topical form is from about 0.1% w/w to about 10 % w/w of the total composition. Preferably, the effective amount of the compound of the invention is 1% w/w of the total composition.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123 and 4,008,719; the disclosures of which are hereby incorporated by reference.

Desirably, each tablet contains from about 200 mg to about 1500 mg of the active ingredient. Most preferably, the tablet, cachet or capsule contains either one of three dosages, about 200 mg, about 400 mg, or about 600 mg of the active ingredient.

When the pharmaceutical composition is formulated into an injectable preparation, in formulating the pharmaceutical composition into the form of a solution or suspension, all diluents customarily used in the art can be used. Examples of suitable diluents are water, ethyl alcohol, polypropylene glycol, ethoxylated isostearyl alcohol, polyoxyethylene sorbitol, and sorbitan esters. Sodium chloride, glucose or glycerol may be incorporated into a therapeutic agent.

The antimicrobial pharmaceutical composition may further contain ordinary dissolving aids, buffers, pain-alleviating agents, and preservatives, and optionally coloring agents, perfumes, flavors, sweeteners, and other drugs.

For topical application, there are employed as non-sprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, e.g. preservatives, antioxidants, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient preferably in combination with a solid or liquid inert carrier material.

A specific embodiment of the invention is the preparation of storage stable compositions of the compounds of the invention of formula I. Such stable compositions can be advantageously made through the use of selective stabilizers. Different stabilizers are known to those skilled in the art of making pharmaceutical compositions. Of special utility for making storage stable compositions of the compound of the invention of formula I, stabilizers such as disodium ethylenediaminetetraacetic acid (EDTA), tromethamine, cyclodextrins such as gamma-cyclodextrin, hydroxy-propyl-gamma-cyclodextrin have been found to be useful.

In a specific embodiment of the invention, the pharmaceutical compositions contain an effective amount of the active compounds of the invention, its derivatives, inclusion complexes, salts or hydrates thereof described in this specification as hereinbefore described in admixture with a pharmaceutically acceptable carrier, diluent or excipients, and optionally other therapeutic ingredients.

The invention is further defined by reference to the following examples describing in detail the preparation of the composition of the present invention as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods may be practiced without departing from the purpose and scope of this invention.

The compounds of this invention are useful antimicrobial agents, effective against various human and veterinary pathogens, similar to the efficacy described for the compounds of US Patent 5,668,286 and EP 0 750, 618 B1.

The test methods used for verifying the antimicrobial action of compound within the scope of this invention are essentially the same as those described in US Patent 5,668,286 and EP 0 750, 618 B1, with the difference that the strains of the organisms used for the MIC determinations are *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12828, *Streptococcus pyogenes* ATCC 19615. The results obtained for the compounds of the invention are in accordance with those

described in the aforementioned patents, with MIC values ranging from 0.5 to > 25.0 for the cited strains. Other organism strains used for this invention are Methicillin Resistant *Staphylococcus aureus* MRSA-32, *Enterococcus faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619, with similar results.

The antimicrobial action of the compounds of this invention was also verified by the Murine Assay procedure (*in vivo*) as described in US Patent 5,668,286 and EP 0 750, 618 B1 for the compounds cited in the aforementioned patents as well as for the instant compounds of the invention. The ED_{50} values obtained for the compounds of the instant invention are found to be in the range of 2.8 mg/kg to 8.2 mg/kg upon oral administration; hence they were as effective as the compounds cited in the aforementioned patents.

A specific embodiment of this invention is that the pharmacokinetic profile of a compound of the invention is such that it permits administration of a dosage schedule which is a much-desired once-a-day dosing, a schedule not so far advocated for the only currently available drug in the market.

We now describe the test method for displaying and verifying the pharmcokinetic profile of the compounds within the scope of this invention which would enable bioavailability of the drug in mammals in such amounts that the dosing can be reduced to once-a-day. The pharmacokinetics of a representative compound of the invention following single intravenous and oral dose administration of the compound in mouse and dog is shown in Table 2. The pharmacokinetic values show their superiority over the reference market drug Linezolid and the best compound/s of the invention disclosed in US Patent 5,668,286 and EP 0 750 618 B1. The values are in support of a potential use of the compounds of the invention for once-a-day treatment.

A further embodiment of this invention is that the once-a-day dosage schedule confirs safety advantages in respect of the phenomenon of myelosuppression described as an attribute of this class of compounds which needs to be avoided.

The test method for verifying the myelosuppression potential is described below. The results are shown in Table 3. The representative compound of the invention provided no significant changes of relative weight ratios of spleen- or thymus-weight to body weight with respect to untreated controls in contrast to for the best compound of US Patent 5,668,286 or EP 0750 618 B1 or for Linezolid, significant changes of relative weight ratios of spleen- or thymus-weight to body weight with respect to untreated controls. Furthermore, the representative compound of the invention provided no significant percentage change in relative reticulocyte count in comparison to values for best compound of US Patent 5,668,286 or EP 0750 618 B1 or for Linezolid.

TEST EXAMPLES

Test Example 1

MIC Test Method .

The in-vitro MIC methods of test compounds were determined essentially as described in US Patent 5,668,286 and EP 0 750 618 B1.

Test Example 2

Murine Assay procedure

The in-vivo ED_{50} values using the test compounds were determined essentially by the method as described in US Patent 5,668,286 and EP 0 750 618 B1.

We also describe below the test methods for determining the pharmacokinetic profile of the compounds, which would enable assessing the bioavailability of the drug in mammals in such amounts that the dosing can be reduced to once-a-day. The pharmacokinetics of a representative compound of the invention following single intravenous and oral dose administration of the compound in dog is shown in **Tables 2 and 3**. The pharmacokinetic parameter values show its superiority over the reference

commercial drug Linezolid (LNZ) and Compound Nos. 30, 3, 7 and 11 of the invention disclosed in US Patent 5,668,286. The values are in support of a potential use of the compounds of the invention for once-a-day treatment.

Test Example 3

Pharmacokinetic studies

Oral (5 mg / kg) and intravenous (5 mg/kg bolus) pharmacokinetic studies were done in dog. Blood samples were collected at time points of 0, 0.08 (not for oral), 0.25, 0.50, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 and 24.0 hours. To facilitate i.v. dosing and collection of blood samples, the dogs were implanted with cannula in cephalic vein. Serum obtained from blood samples was used for HPLC-based analysis.

Serum samples were extracted by solid phase extraction technique using Water's OASIS HLB cartridges. An HPLC-Diode array detection system was used for analysis. Prepared samples were chromatographed on a YMC-AM reversed phase column (150X4.6mm ID; 5µm) using an isocratic mobile phase acetate buffer (50 mmol ammonium acetate pH 6.6) acetonitrile, 66:34 % v/v (for a representative compound of the invention, 68:32 % v/v for compound Nos. 30, 3, 7 and 11 of US Patent 5,668,286, and 75:25 % v/v for linezolid) at a flow rate of 1 ml/min, measured at λ_{max} 254 nm. Independently prepared analytical standards and quality control samples were analyzed with each set of unknown samples. The calculated pharmacokinetic parameters are shown in **Tables 2 & 3** below.

Table 2: Comparative PK Parameters following Single Oral dose in Beagle Dog

(5 mg/kg, *p.o.* administered in cyclodextrin solution (5-10% w/v water))

PK Parameter	Rep. Compound Of the invention	Compound No. 30 of US Patent 5,668,286	Compound No. 3 of US Patent 5,668,286	Compound No. 7 of US Patent 5,668,286	Compound No. 11 of US Patent 5,668,286	LNZ
Cmax (μg/ml)	5.66	5.31	1.52	NIL	NIL	4.97
AUC(0-infinity) μg.hr/ml	92.62	51.78	2.74	NIL	NIL	32.67
T1/2 (hr)	10.79	6.68	1.37	NIL	NIL	3.62

Table 3: Comparative PK Parameters following Single I.V. Bolus Dose in Beagle Dog

(15 mg/kg bolus administered in cyclodextrin solution (5-10 % w/v water))

PK Parameter	Rep. Compound of the invention	Compound No. 30 of US Patent 5,668,286	Compound No. 3 of US Patent 5,668,286	Compound No. 7 of US Patent 5,668,286	Compound No. 11 of US Patent 5,668,286	LNZ (n=1)
Cmax (μg/ml)	8.28	7.64	6.19	NIL	4.15	7.16
AUC(0-infinity) μg.hr/ml	107.29	48.47	7.80	NIL	1.32	24.62
T1/2 (hr)	12.95	6.71	0.98	NIL	0.16	2.41

We also, furthermore, describe below the test methods to determine the potential myelosuppression activity of the compounds of the invention in rats. In Table 4 is provided the values of the parameters assessed to determine the myelosuppressive activity potential. The results indicate that the compounds of the invention are devoid of myelosuppressive potential.

Test Example 4

Myelosuppressive Potential:

Method: A group of 6 Wistar rats (3 male and 3 female) were exposed to a representative compound of the invention or to compound No.30 of US Patent 5,668,286 by oral route at a BID dose of 25 mg/kg (total dose 50 mg/kg/day) for 14 consecutive days. Linezolid (LNZ) was used as a comparator drug and was administered to rats using an identical protocol. Vehicle treated controls were maintained using identical experimental conditions. The treated as well as control rats were sacrificed 24 hr after the last dose.

One parameter measured was the spleen to body weight ratio and thymus to body weight ratio in treated versus control animals.

The spleen and thymus were trimmed free of fat and other contiguous organs/tissues and were weighed in an analytical balance (Sartorious BP 210). The spleen to terminal body weight ratio and the thymus to terminal body weights ratio was calculated to provide the respective relative weights. The ratio value of the respective relative weight of a treated animal versus the relative weight of a control animal is provided in **Table 4.** The myelosuppressive potential of a compound is inversely proportional to the ratio value. For instance a ratio less than 0.75 indicates myelosuppressive potential. The results shown in Table 4 clearly indicate that the representative compound of the invention is devoid of immunosuppression potential in contrast to the reference compound Linezolid.

A second parameter measured was the change in reticulocyte count, for which the following method was used.

Reticulocyte Counts:

Blood Collection

Blood was collected on day 15 (24 hours after the last dose administration) from all the treated as well as control rats by retro-orbital sinus puncture using clean glass rat capillary tubes. The blood was collected in sterile clean and anticoagulated Eppendorf microtubes. EDTA was used as the anticoagulant (conc.: 2mg/10ml).

Staining Procedure

The staining solution of New Methylene Blue (NMB) was prepared in iso-osmotic phosphate buffer pH 7.4 (150mM) saline to achieve a concentration of 0.6% (w/v) and the stock stored in an amber colored glass bottle at 2-6^{o}C.

Counting Procedure

3 slides/animal were prepared according to *NCCLS* staining procedure for reticulocyte staining and counting. The collected blood was mixed gently by inverting the tube 2-3 times and freshly prepared stock of 0.6% (w/v) NMB was mixed with the blood at equal volume in microtube and incubated at 37^{o}C for 20 minutes. The stained blood specimen was smeared evenly on a clean, dry and grease-free slide with the help of a spreader. 3 slides per rat were prepared, allowed to dry in warm air and mounted with the help of DPX solution and a clean cover slip. Counting of erythrocytes and reticulocyte was done for each slide using a microscope under 100X magnification (oil immersion). The percentage presence of reticulocyte was determined in 1000 erythrocytes and was expressed in terms of percentage of reticulocytes over erythrocytes. The ratio of the percentage reticulocytes in treated animals versus controlled animals is provided in Table 4 as a ratio value of the percentages. The myelosuppressive potential is inversely proportional to the ratio value. For instance a ratio less than 0.75 indicates myelosuppressive potential. The results provided in Table 4 clearly indicate that the representative compound of the invention is devoid of immunosuppressive potential. (Reference: T*he National Committee for Clinical Laboratory Standards (NCCLS) : Methods for Reticulocyte Counting (Flow Cytometry and Supravital Dyes) ; Approved*

Guideline. NCCLS Document H44-A (ISBN 1-56238-302-7). NCCLS 940 West Vally Road, Suit 1400, Wayne, Pennsylvania 19087-1898, USA, 1997. Page No. 04)

Table 4 – Ratio value of spleen weight / body weight and thymus weight / body weight of treated animal versus control animal, and ratio of percentage reticulocytes of treated animal versus control animal

Compounds	Relative Weights Ratio		% Ratio
	Spleen	Thymus	Retics
Representative Compound of the invention	0.94 (±0.044)	1.172 (±0.111)	1.04 (±0.2)
LNZ	0.46 (±0.032)	0.46 (±0.043)	0.43 (±0.071)

(Figures in parenthesis indicates ±SE of mean values) N = 6 (3 male + 3 female rats/group)

Values in each of the first two columns above represent ratio of relative weight (calculated organ to body weight ratio) of spleen or thymus in drug treated animals v/s control animals. A ratio of 0.75 and above indicates minimal changes in the weight of the organs and the value of 1 suggests absence of adverse drug effect on spleen or thymus. The "Retics" column provides ratio of percentage reticulocytes in treated v/s percentage reticulocytes in control rats.

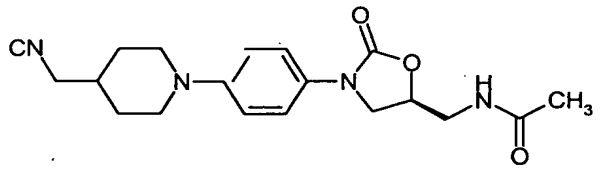
It should be noted here that none of the compounds of this invention nor pharmaceutically acceptable complexes or salts thereof have been found to have toxicity that would cause any problem.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples are provided to further illustrate this invention but they should not be taken as limiting.

Example 1

(S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide:



The compound was prepared according to the method –1. Thus diethyl cyanomethyl phosphonate (10g, 0.56 mol), lithium bromide (4.87g, 0.056 mol) and triethyl amine (10.30 g, 0.10 mol) in 250 ml tetrahydrofuran was stirred for 30 minutes at a temperature 35 ^{O}C. To the suspension (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (17g, 0.51 mol) in 50 ml tetrahydrofuran was added under stirring. The reaction progress was monitered on TLC. After completion of the reaction, the reaction mixture was neutralized with 0.5 N hydrochloric acid and extracted with 500 ml ethyl acetate twice. The combined organic extract was dried over sodium sulphate, concentrated under vacuum to give crude product which upon silica gel column chromatography furnished the titled product in (15.92 g) 88% yield.

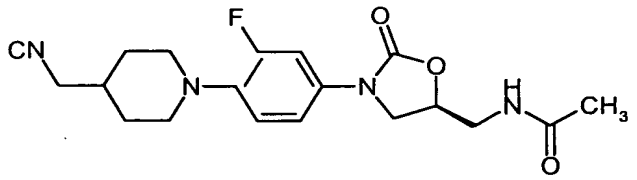
Mp. 150-152 °C

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.42 -1.60 (m, 2H), 1.75-2.00 (m, 3H), 2.05 (s, 3H), 2.90 (d, 2H), 2.75 (m, 2H), 3.50-3.80 (m, 5H), 4.05 (m, 1H), 4.75 (m, 1H), 6.15 (t, 1H), 6.90 (dd, 2H), 7.40 (dd, 2H)

MS (ES^{+}): m/z = 357.

Example 2

(S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide



The compound was prepared as per procedure described in Example –1 by using (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide in 89 % yield.

Mp. 220-222 °C

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.49 (m, 2H), 1.75-2.00 (m, 3H), 2.05 (s, 3H), 2.30-2.41 (m, 2H), 2.60-2.80 (m, 2H), 3.38-3.50 (m, 2H), 3.60-3.81 (m, 3H), 3.95-4.10 (m, 1H), 4.70-4.85 (m, 1H), 6.41-6.59 (m, 1H), 6.90 (dd, 1H, *J* = 9.2, 9.2 Hz), 7.10 (dd, 1H, *J* = 2.2, 2.2 Hz), 7.41 (dd, 1H, *J* = 2.2, 14.0 Hz)

MS (ES^+): m/z = 375.

Example 3A

Preparation of inclusion complex of (S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide with 3-hydroxy-propyl-B-cyclodextrin (3-HP-B-CD) in 1: 1.2 molar ratio:

3-HP-B-CD (485 mg, 0.316 mmol) was dissolved in a 10 ml distilled water . To the clear solution, (S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (100 mg, 0.26 mmol) was charged at 32^{0}C under stirring. The reaction mixture was stirred vigorously at a temperature 32^0 C for 1 hours. The reaction mixture was evaporated to dryness under vacuum below 45 ^{0}C to provide a white solid in 575 mg quantity in quantitative yield.

Differential Scanning Colorimetry (DSC):

The DSC spectrum of the inclusion complex did not show endotherm at 168 ^{0}C, however the physical mixture in same molar ratio has shown the endotherm at 168.0 ^{0}C.

Powder X-ray diffractogram (XRPD):

The XRPD of the inclusion complex showed amorphous nature of the complex where a hump was observed. However the powder X-ray difractogram of a physical mixture in same molar ratio showed peaks at 10.54, 17.60 and 21.32 (2θ values).

Example 3B

Preparation of inclusion complex of (S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide with 3-hydroxy-propyl-B-cyclodextrin (3-HP-B-CD) in 1 : 2 molar ratio

3-HP-β-CD (12.30 gm, 8.03 mmol) was dissolved in a 150 ml distilled water . To the clear solution, (S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide (1.5 gm, 4.01 mmol) was charged at 30^{0}C under stirring. The resultant suspension was warmed to 48 ^{0} C for 2 hours to obtain a clear solution. The clear solution was cooled to a temperature at 25 ^{0}C and allowed to stand for 16 hours. The reaction mixture was filtered and filtrate was evaporated to dryness under vacuum below 45 ^{0}C temperature to provide a white solid in 13.0 gm quantity (90% yield).

Differential Scanning Colorimetry (DSC):

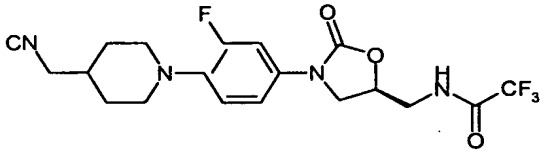
The DSC spectrum of the inclusion complex did not show endotherm at 168 ^{0}C, however the physical mixture in same molar ratio showed endotherm at 168.0 ^{0}C.

Powder X-ray diffractogram (XRPD):

In the XRPD of the inclusion complex showed amorphous nature of the complex. However the powder X-ray difractogram of a physical mixture in same molar ratio showed peaks at 10.68, 17.78 and 21.44 (2θ values).

Example 4

(S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-trifluoroacetamide



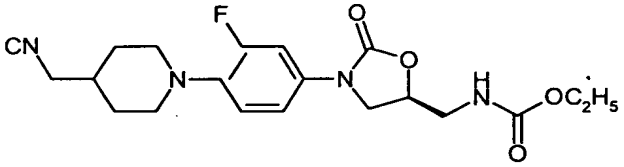
The compound was prepared as per procedure described in Example –1 by using (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}-trifluoroacetamide in 71 % yield.

Mp. 120-123 °C

MS (ES^+): m/z = 429.

Example 5

(S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-ethylcarbamate



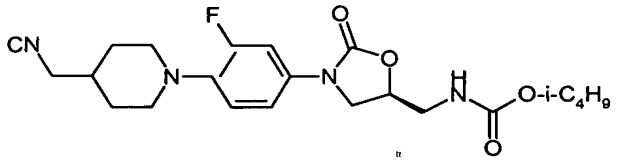
The compound was prepared as per procedure described in Example –1 by using (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}-ethylcarbamate in 67 % yield.

Mp162-164°C

MS (ES^+): m/z = 375.

Example 6

(S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-isobutylcarbamate



The compound was prepared as per procedure described in Example –1 by using (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}-isobutylcarbamate in 79 % yield.

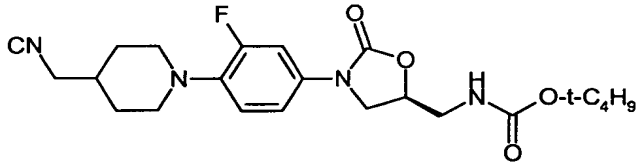
Mp194-196 °C

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.85 (dd, 6H), 1.50-1.70 (m, 2H), 1.80-2.0 (m, 4H), 2.40 (m, 2H), 2.60-2.80 (m, 2H), 3.40-3.60 (m, 4H), 3.70-3.90 (m, 3H), 4.05 (m, 1H), 4.70-4.85 (m, 1H), 6.90 (dd, 1H), 7.10 (dd, 1H), 7.40 (dd, 1H)

MS (ES^+): m/z = 433.

Example 7

(S)-N-{3-[4-(4-cyanomethyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-t-butylcarbonylamide



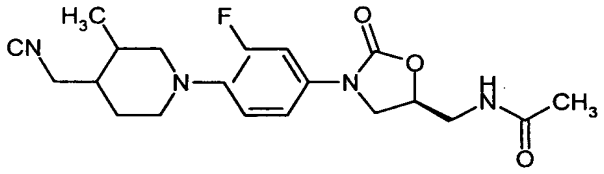
The compound was prepared as per procedure described in Example –1 by using (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}- t-butylcarbamate in 71 % yield.

Mp. 192-194 °C

MS (ES^+): m/z = 433.

Example 8

(S)-N-{3-[4-((4-cyanomethyl)-3-methyl-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide



The compound was prepared as per procedure described in Example –1 by using (S)-N-{3-[4-((4-oxo-3-methyl)-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide in 75 % yield.

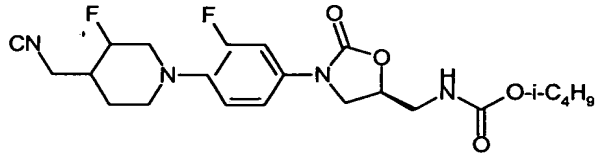
M.P. = 148-149°C

^{1}H NMR (200 MHz, $CDCl_3$) ppm: 7.42 (dd, 1H, J = 13.5, 1.8 Hz), 7.1 (dd, 1H, J = 8.0, 1.8 Hz), 6.90 (t, 1H, J = 8.0 Hz), 6.03 (t, 1H, D_2O exchangeable), 4.7-4.8 (m, 1H), 4.01 (t, 1H, J = 8.0 Hz), 3.45-3.80 (m, 3H), 3.1-3.35 (m, 2H), 2.7-2.9 (m, 2H), 2.38 (d, 2H, J = 7.0 Hz), 2.1-2.2 (m, 1H), 2.05 (s, 3H), 1.70-1.80 (m, 3H), 1.10 (d, 3H, J = 7.0 Hz).

MS (ES^+): m/z = 389.

Example 9

(S)-N-{3-[4-((4-cyanomethyl)-3-fluoro-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-isobutylcarbamate



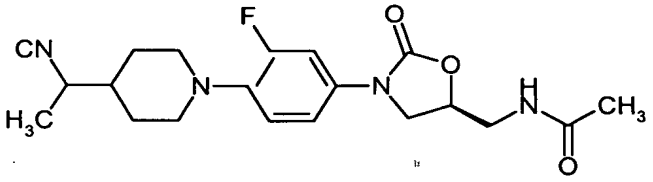
The compound was prepared as per procedure described in Example –1 by using (S)-N-{3-[4-((4-oxo-3-fluoro)-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}-isobutylcarbamate in 81 % yield.

Mp. 146-148 °C

MS (ES^+): m/z = 451.

Example 10

(S)-N-{3-[4-(4-(1-cyanoethyl)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide



The compound was prepared as per procedure described in Example –1 by using diethyl-1-cyanoethyl phosphonate and (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide in 87 % yield.

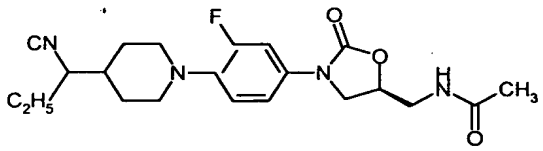
M.P. = 147-148°C

^{1}H NMR (200 MHz, $CDCl_3$) ppm: 7.41 (dd, 1H, J= 13.8, 1.8 Hz), 7.06 (dd, 1H, J= 8/0. 1.8 Hz), 6.88 (t, 1H, J = 8.0 Hz), 6.00 (t, 1H, D_2O exchangeable), 4.7-4.8 (m, 1H), 4.02 (t, 1H, J = 7.0 Hz), 3.60-3.80 (m, 3H), 3.42 (bd, 2H), 2.45-2.70 (m, 3H), 2.03 (s, 3H), 1.6-1.8 (m, 5H), 1.38 (d, 3H, J =6.5 Hz).

MS (ES^+): m/z = 389

Example 11

(S)-N-{3-[4-(4-(1-cyanopropyl)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide



The compound was prepared as per procedure described in Example –1 by using diethyl-1-cyanopropyl phosphonate and (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide in 88 % yield.

Mp. 185-186 °C

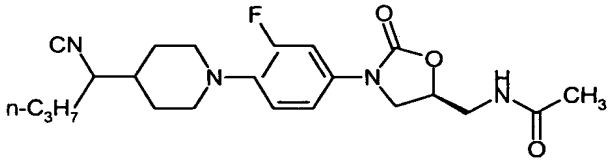
^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.18 (t, 3H, *J* = 4.8Hz),1.60-1.89 (m, 4H), 2.05 (s, 3H), 2.30-2.50 (m, 1H), 2.60-2.80 (m, 2H), 3.39-3.60 (m, 2H), 3.60-3.82 (m, 3H), 3.90-4.10

(m, 1H), 4.70-4.85 (m, 1H), 5.95-6.19 (m, 1H), 6.90 (dd, 1H, *J* = 9.2, 9.2 Hz), 7.05 (dd, 1H, *J* = 2.2, 2.2 Hz), 7.41 (dd, 1H, *J* = 2.2, 14.0 Hz).

MS (ES^+): m/z = 403.

Example 12

(S)-N-{3-[4-(4-(1-cyanobutyl)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide



The compound was prepared as per procedure described in Example –1 by using diethyl-1-cyanobutyl phosphonate and (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide in 82 % yield.

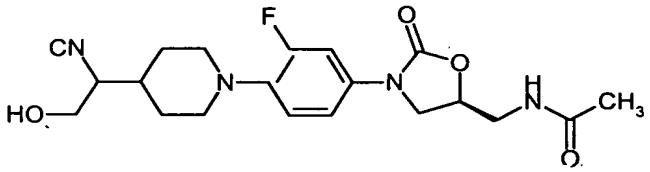
Mp. 180-182 °C

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 0.82-1.10 (m, 2H,), 1.20-1.40 (m, 2H), 1.55-1.80 (m, 7H), 2.05 (s, 3H), 2.40-2.80 (m, 3H), 3.40-3.55 (m, 2H), 3.60-3.80 (m, 3H), 3.95-4.10 (m, 1H), 4.70-4.85 (m, 1H), 6.15-6.25 (m, 1H), 6.90 (dd, 1H, *J* = 9.2, 9.2 Hz), 7.05 (dd, 1H, *J* = 2.2, 2.2 Hz), 7.44 (dd, 1H, *J* = 2.2, 14.0 Hz).

MS (ES^+): m/z = 417.

Example 13

(S)-N-{3-[4-(4-(1-cyano-2-hydroxyethyl)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide



The compound was prepared as per procedure described in Example –1 by using diethyl-1-cyano-2-hydroxyethyl phosphonate and (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide in 62 % yield.

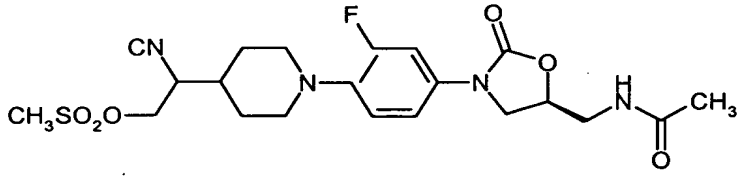
M.P. = 182-184°C

^{1}H NMR (200 MHz, DMSO-d_6) ppm: 8.22 (1H, t, D_2O exchangeable), 7.43 (dd, 1H, J = 13.8, 1.8Hz), 7.18 (dd, 1H, J = 8.0, 1.8 Hz), 7.05 (t, 1H, J = 8.0 Hz), 5.23 (bt, 1H, D_2O

exchangeable), 4.30-4.80 (m, 1H), 4.05 (t, 1H, J =7.0 Hz), 3.60-3.75 (m, 3H), 3.25-3.40 (m, 4H), 2.82 (m, 1H), 2.60 (bt, 2H), 1.82 (s, 3H), 1.35-1.82 (m, 5H).
MS (ES^+): m/z = 405

Example 14

(S)-N-{3-[4-(4-(1-cyano-2-methanesulfonyloxyethyl)--piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide

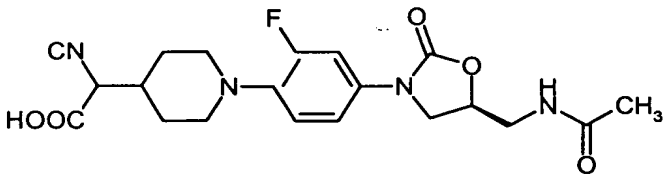


The compound was prepared stirring the compound from Example –13 and methanesulphonyl chloride, triethyl amine in dichloromethane at a temperature between 0- 10 0C for 2 hours and purifying the crude product on silica gel column chromatography in 87 % yield.

M.P. = 136-138°C
^1H NMR (200 MHz, $CDCl_3$) ppm: 7.42 (dd, 1H, J= 13.8, 2.0 Hz), 7.08 (dd, 1H, J= 8.0, 2.0 Hz), 7.0 (t, 1H, J = 8.0 Hz), 6.1 (t, 1H, D_2O exchangeable), 4.7-4.85 (m, 1H), 4.42 (d, 2H, J = 7.0 Hz), 4.02 (t, 1H, J = 7.0 Hz), 3.60-3.80 (m, 3H), 3.45 (bd, 2H), 3.18 (s, 3H), 2.95 (q, 1H, J = 7.0 Hz), 2.75 (bt, 2H), 2.05 (s, 3H), 1.65-1.85 (m, 5H).
MS (ES^+): m/z = 483

Example 15

(S)-N-{3-[4-(4-(1-cyano-1-hydroxycarbonyl)--piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide



The compound was prepared as per procedure described in Example –1 by using diethyl-1-cyano-1-hydroxycarbonyl phosphonate and (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide in 62 % yield.

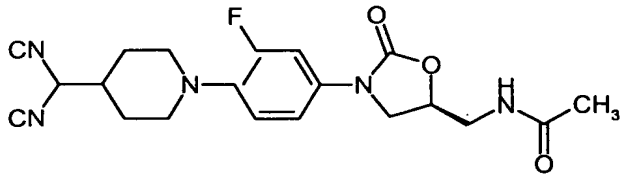
M.P. = 198-200°C

^{1}H NMR (200 MHz, DMSO-d_6) ppm: 8.25 (1H, t, D_2O exchangeable), 7.43 (dd, 1H, J = 13.3, 1.8Hz), 7.15 (dd, 1H, J = 8.0, 1.8 Hz), 7.03 (t, 1H, J = 8.0 Hz), 4.6-4.8 (M, 1H), 3.60-4.1 (m, 4H), 3.2-3.4 (m, 3H), 2.75 (bt, 2H), 1.9 (s, 3H), 1.45-1.8 (m, 5H).

MS (ES^+): m/z = 419

Example 16

(S)-N-{3-[4-(4-(1,1-dicyanomethyl)-piperidin-1-yl)-3-fluoro-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide



The compound was prepared as per procedure described in Example –1 by using diethyl-1,1-dicyanomethyl phosphonate and (S)-N-{3-[4-(4-oxo-piperidin-1-yl)-3-fluoro phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide in 60 % yield.

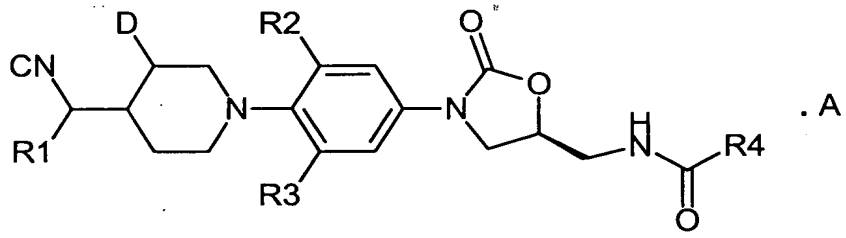
Mp. 223-225 °C

^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.75-1.90 (m, 2H), 2.00 (s, 3H), 2.05-2.10 (m, 2H), 2.61-2.82 (m, 1H), 3.41-3.62 (m, 2H), 3.65-3.85 (m, 3H), 4.00-4.20 (m, 1H), 4.70-4.90 (m, 1H), 6.05 (t, 1H, *J* = 5.9Hz),), 6.90 (dd, 1H, *J* = 9.2, 9.2 Hz), 7.10 (dd, 1H, *J* = 2.2, 2.2 Hz), 7.41 (dd, 1H, *J* = 2.2, 14.0 Hz).

MS (ES+): m/z = 400.

CLAIMS

The present invention provides cyanoalkylpiperidinophenyl oxazolidinones represented by the general Formula-I



. A

Formula-I

Wherein,

R_1 is

-H;

C1-C8 alkyl;

substituted alkyl;

-COOH;

-CN.

R_2 and R_3 are the same or different and are H or fluorine;

R4 is

H;

C1-C8 alkyl;

C1-C8 alkoxy.

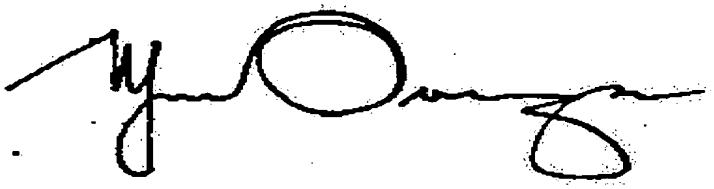
D is

H;

C1-C8 alkyl;

fluorine.

A is
nothing;
complex forming agent;
organic base;
amino acid.



Dated this 17th day of April 2003
Place: Aurangabad

Dr. N J de Souza
Director-R&D